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Synthesis and Physicochemical Properties of 3-Fluorocyclobutylamines

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Hitherto unknown *cis*- and *trans*-3-alkyl- and 3-aryl-3-fluorocycobutylamines have been synthesised selectively from 3-oxocyclobutane carboxylic acid in six or seven steps. Comparison of their pK_a and log D values with those of the fluorine-free parent compounds showed acidification by about 0.8 units, irrespective of the stereochemistry. This indicates that there are no through-space interactions between fluorine and the amino function – a conclusion that was supported by the results of X-ray analysis. Fluorinated *trans*-compounds were found to be more lipophilic ($\Delta \log P \approx 1$) compared with the non-fluorinated analogues, whereas the difference was marginal for *cis* isomers.

Introduction

One of the most important challenges in modern drug discovery is the identification of unusual scaffolds that provide functional but unused chemical space.[1] Among recent drug candidates, small-ring systems including cyclopropanes, cyclobutanes, and azetidines have become abundant. During last decades, building blocks involving these cycles have been increasingly used both to "decorate" side chains of an active molecule and to position a required steric restriction on the core structure.[1,2]

Among the cyclic systems, 1,3-disubstituted cyclobutanes possess attractive features for drug discovery because they are achiral due to the presence of a symmetry plane; this attribute makes them convenient targets from the synthetic point of view. Often the corresponding diastereomers can be either synthesised selectively or easily separated. Moreover, they are valuable restricted mimics of alkyl chains. This concept was successfully used to design new analogues of natural amino acids[3] as well as 3D isosters of the 1,4-disubstituted phenylene moiety.[4] Several promising drug candidates such as the selective HMT-inhibitor EPZ-5676,[5] the IGF-1R-inhibitor Linsitinib,[6] the 11β-HSD-1 inhibitor MK-0916,[7] and the histamine H_3 receptor antagonist PF-03654746[4] contain 1,3-disubstituted cyclobutanes (Figure 1). The latter two compounds are examples of successful application of 3-fluorocyclobutanes. In both cases, fluorine was introduced to improve the pharmacokinetic properties. This reflects the common application of fluorine as a valuable tool for hit and lead optimization in modern drug discovery.[8] The success of fluorinated cyclobutanes in drug discovery stimulated the development of synthetic

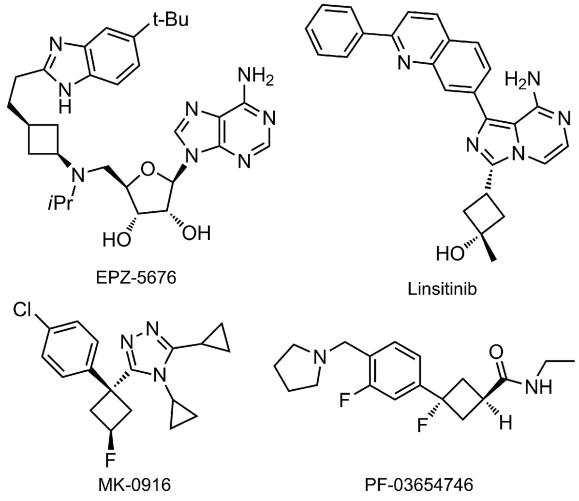

Figure 1. Drug candidates bearing 1,3-disubstituted cyclobutane moieties.

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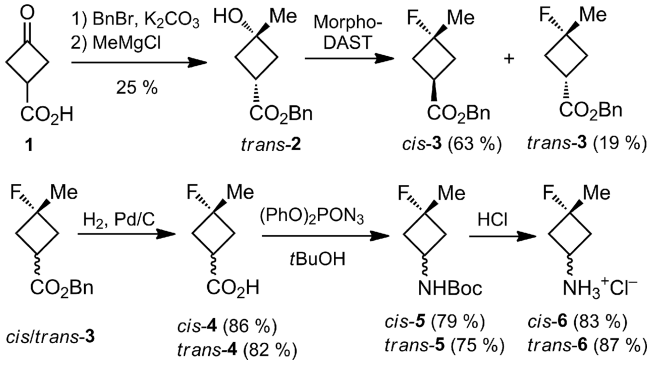
methods towards diverse new building blocks containing this moiety.[9]

Herein, we present the synthesis of hitherto unknown 3-alkyl- and 3-aryl-3-fluorocyclobutylamines as potential building blocks for medicinal chemistry, and we explore the effect of fluorine on crucial physicochemical parameters such as pK_a and log P.[10]

Results and Discussion

Synthesis

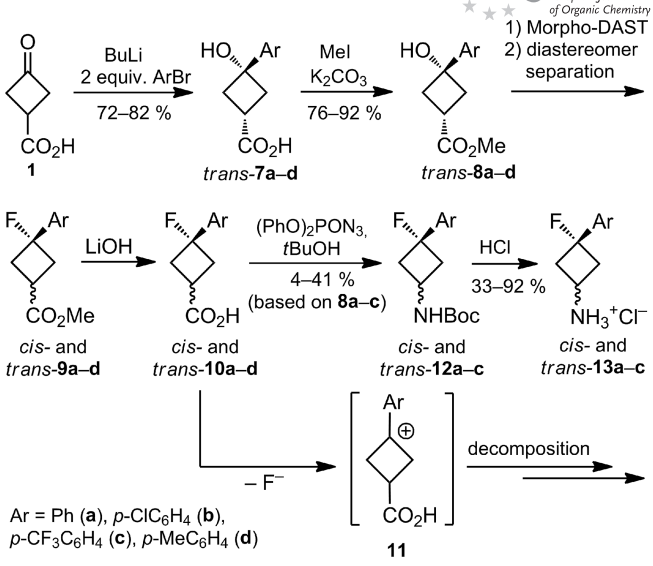
Methylated compounds *cis*- and *trans*-**6** were synthesised starting from commercially available ketoacid **1** as depicted in Scheme 1. The first two steps (synthesis of benzyl ester and Grignard reaction with MeMgCl) were carried out according to described procedures.[11] The pure diastereomer, *trans*-**2**, was obtained after chromatographic purification. Subsequent deoxyfluorination using morpho-DAST proceeded with incomplete inversion of configuration and gave a 3:1 mixture (^{1}H NMR analysis) of diastereomers *cis*-**3** and *trans*-**3**.[12] The mixture was separated by column chromatography. Subsequent steps (hydrogenolysis, Curtius rearrangement, and Boc-deprotection) were carried out starting from pure diastereomers *cis*-**4** and *trans*-**4**. The corresponding diastereomerically pure amines *cis*-**6** and *trans*-**6** were obtained as hydrochlorides in 8.9 and 2.5% overall yield, respectively (based on **1**). The relative configuration of amines *cis*-**6** and *trans*-**6** was confirmed by NOE experiments.



Scheme 1. Synthesis of amines *cis*-**6** and *trans*-**6**.

A similar method was used for the synthesis of 3-aryl-3-fluorocyclobutylamines **13**.[4] Accordingly, unprotected keto acid **2** was treated with an excess of aryllithium reagent, which was generated in situ from the corresponding aryl bromide and butyllithium (Scheme 2).

Thus, compounds *trans*-**7a**–**d** were obtained in good yields and with good diastereoselectivities (*trans*/*cis* ratio ca. 9:1). After isolation and purification, pure diastereomers *trans*-**7a**–**d** were subjected to esterification with MeI/K_2CO_3 to give the corresponding esters *trans*-**8a**–**d**, which were treated with morpho-DAST. Similar to the deoxyfluorination of *trans*-**2**, *trans*-**8a**–**d** also gave mixtures of diastereomers *cis*- and *trans*-**9a**–**d** (ratio 2:1), which were separated by column chromatography and used for subsequent hydrolysis. Unexpectedly, most compounds decomposed during solvent evaporation. Only *trans*-**9b** and *cis*/*trans*-**9c** were stable and were obtained as pure solids; all other esters were obtained as concentrated solutions, which were used for the next step without purification. Acids *cis*/*trans*-**10a**,**b**,**d** were also unstable in pure form and were likewise isolated as solutions (ca. 50% in EtOAc/hexane). Conceivably, decomposition occurred through HF elimination via the corresponding carbocations **11**. Moreover, during saponification of diastereomerically pure esters *cis*-**9d** and *trans*-**9d**, partial epimerization took place, giving 3:1 mixtures of *cis*/*trans*-**10d** in both cases.



Scheme 2. Synthesis of *cis*- and *trans*-**13a**–**d** and assumed decomposition pathway for intermediates **10a**–**d**.

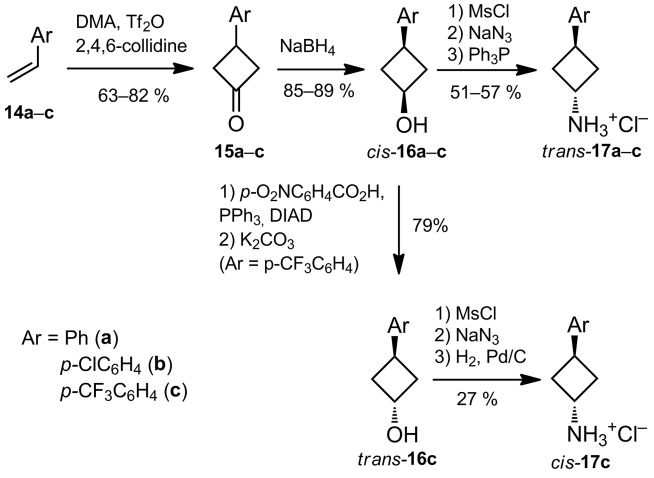
In contrast, acids *cis*-**10c** and *trans*-**10c**, bearing the electron-withdrawing CF_3 group, are stable solids. Presumably, in this case, HF elimination does not take place because of less favoured formation of carbocation **11c**, which is supposed to be the key intermediate of HF elimination and subsequent decomposition.

Isolated concentrated solutions of diastereomerically pure acids *cis*- and *trans*-**10a**–**c** as well as the mixture of *cis*/*trans*-**10d** were immediately subjected to Curtius rearrangement. The yields of the reactions were probably also dependent on the stability of acids **10**. Thus, in case of the mixture of the least stable compounds *cis*/*trans*-**10d**, Curtius rearrangement led to a complex mixture of products with a small amount of Boc-amines *cis*/*trans*-**12d**, which were not isolated. Therefore, no attempts to synthesise the corresponding amines *cis*/*trans*-**13d** were undertaken. In case of Curtius rearrangement of *cis*- and *trans*-**10a** (Ar = Ph), yields of *cis*- and *trans*-**12a** were 14 and 4%, respectively (based on *trans*-**8a**), whereas in the case of the more stable *cis*-**10b**,**c** and *trans*-**10b**,**c**, yields for this stage were higher (36–41 and 14–18%, respectively).

Boc deprotection led to the formation of amine hydrochlorides *cis*- and *trans*-**13a**–**c** in moderate to high yields. The overall yields of *cis*- and *trans*-**13a**–**c** based on **1** were 3.5–25 and 0.7–8%, respectively. Whereas hydrochlorides

cis- and *trans*-**13b**,**c** were stable compounds, *cis*- and *trans*-**13a** partially decomposed during storage (accompanied by elimination of HF, similar to *cis*/*trans*-**11a**,**b**,**d**, *cis*-**9a**,**b**,**d**, and *trans*-**9a**,**d**).

To assess the influence of fluorine on the properties of *trans*-**13b**,**c** the corresponding non-fluorinated parent compounds *trans*-**17a**–**c**[12] were synthesised by using a previously described method[13] (Scheme 3).



Scheme 3. Synthesis of *cis*-**17c** and *trans*-**17a**–**c**.

Thus, commercially available styrenes **14a**–**c** were easily transformed into the corresponding cyclobutanones **15a**–**c** by [2+2]-cycloaddition with the ketene iminium salt generated from dimethyl acetamide (DMA).[13b] Diastereoselective reduction by $NaBH_4$ led to the formation of *cis*-**16a**–**c**.[12] Subsequent mesylation and nucleophilic substitution with complete inversion of configuration led to the corresponding *trans*-azides, which were reduced by using triphenylphosphine to give the target amines *trans*-**17a**–**c** as hydrochlorides. The overall yields (based on **14a**–**c**) were 28–38%.

Compound *cis*-**17c**,[12] which possesses the same spatial arrangement of aryl and amine groups as *cis*-**13c**, was obtained similarly, starting from alcohol *cis*-**16c**. This compound was subjected to standard Mitsunobu protocol to invert stereochemistry,[14] giving alcohol *trans*-**16c**.[12] For the last stage, hydrogenation on Pd/C was found to be more convenient than reduction using triphenyl phosphine. However, the method could not be used for the synthesis of chloro compound *cis*-**17b** because of partial C–Cl bond hydrogenolysis.

Physical Chemical Properties

Having both isomers of the fluorinated cyclobutanes *cis*/*trans*-**6** and *cis*/*trans*-**13b**,**c** in hand, we wanted to study the influence of fluorine on the basicity of the NH_2 group. Well-studied involvement of fluorine in weak bonds, which are considered as charge–dipole interactions[10d,15] or hydrogen bonds,[16] often lead to significant change of pK_a values.[10a–10d] In the case of compounds **6** and **13**, we expected to observe this kind of interaction for *trans* isomers, for which fluorine and NH_3^+ are in *cis*-orientation to each other.[12] Indeed, we observed a significant difference in the ^{19}F NMR chemical shift values of *cis*-**6**,**13a**–**c** (δ_F = –142 to –149 ppm) and *trans*-**6**,**13a**–**c** (δ_F = –122 to –125 ppm) and therefore suspected that the assumed interaction, present in one but absent in the other isomer, would be reflected in a significant difference in the pK_a values of the *cis* and *trans* isomers.

Unexpectedly, pK_a values for pairs of isomers *cis*/*trans*-**6** and *cis*/*trans*-**13b**,**c** were very similar (Table 1). This fact could mean that there are no intramolecular interactions between the amino groups and fluorine atoms. This conclusion was indirectly confirmed by X-ray data of compounds *cis*- and *trans*-**12b** (Figure 2).[17]

Table 1. Measured pK_a and log *D* of obtained compounds *cis*-**6**,**13b**,**c**,**17c** and *trans*-**6**,**13a**–**c**,**17a**–**c** compared with *cis*/*trans*-**18a**–**c**.[20]

Entry	Compound	pK_a (standard deviation)[a]	log *D*, pH 7.4 (standard deviation)[a]	log *P*[b]
1	*cis*-**6**	9.25 (0.04)	–0.11 (0.03)	1.75
2	*trans*-**6**	9.24 (0.03)	–0.36 (0.10)	1.49
3	*cis*-**13a**	–[c]	–[c]	
4	*trans*-**13a**	8.91 (0.03)	–[d]	–
5	*cis*-**13b**	8.83 (0.01)	1.43 (0.04)	2.88
6	*trans*-**13b**	8.68 (0.02)	2.84 (0.06)	4.14
7	*cis*-**13c**	8.71 (0.13)	1.79 (0.01)	3.12
8	*trans*-**13c**	8.66 (0.04)	3.14 (0.02)	4.42
9	*trans*-**17a**	9.65 (–[e])	–[d]	–
10	*trans*-**17b**	9.53 (0.08)	0.93 (0.02)	3.06
11	*cis*-**17c**	9.45 (–[e])	1.31 (0.06)	3.36
12	*trans*-**17c**	9.50 (0.02)	1.15 (0.02)	3.25
13	*cis*-**18a**[f]	6.98	1.78	–
14	*trans*-**18a**[f]	7.35	1.53	–
15	*cis*-**18b**[f]	6.81	2.66	–
16	*trans*-**18b**[f]	7.19	2.23	–
17	*cis*-**18c**[f]	6.60	3.13	–
18	*trans*-**18c**[f]	7.00	2.66	–

[a] In general, at least three measurements of pK_a and log *D* were carried out. [b] log *P* values were calculated by using the formula $\log P = \log D_{7.4} + \log(1 + 10^{pKa - 7.4})$.[19] [c] p$K_a$ and log *D* were not measured because of the instability of the compound. [d] log *D* was not measured. [e] Only one measurement was carried out. [f] pK_a and log *D* data were taken from the literature.[20]

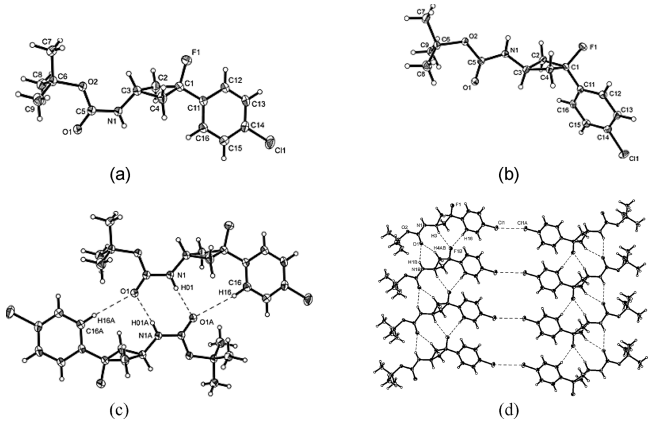


Figure 2. Crystal structures of *cis*-**12b** (a) (thermal ellipsoids are shown with 30% probability); *trans*-**12b** (b) (thermal ellipsoids are shown with 50% probability), and intermolecular contacts identified in *cis*-**12b** (c) and *trans*-**12b** (d).[17]

Considering conformations of *N*-Boc-protected compounds *cis*/*trans*-**12b** determined by X-ray analysis, and assuming similar conformations for ammonium ions *cis*- and *trans*-**6**,**13**, we can assume the reason for essentially identical acidity for the pairs of *cis*- and *trans*-**6**,**13** (Figure 3). Thus, according to X-ray data of *cis*-**12b**, aryl and Boc-amino groups occupy pseudo-equatorial (e′) positions whereas fluorine is located in the pseudo-axial position (a′). The same conformation **A** is also assumed to be the most favourable for *cis*-**6**,**13**, whereas conformation **B** is expected to be less favourable for steric reasons. This is consistent with the observed ^{19}F NMR chemical shifts, for which pseudo-axial fluorine is expected to be more shielded compared with pseudo-equatorial fluorine.[18]

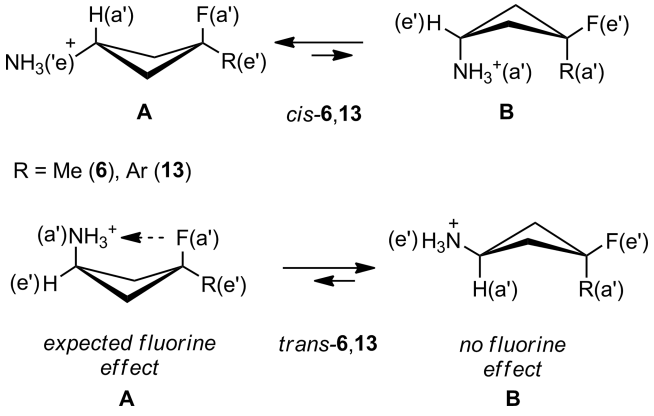


Figure 3. Favourable and unfavourable conformations of *cis*- and *trans*-**6**,**13**.

In the case of *trans*-**12b**, the fluorine and Boc-amino groups occupy pseudo-equatorial positions and are distant from each other in conformation **B**, which is supposed to be favourable also for *trans*-**6**,**13**. Again, this is in agreement with the observed downfield ^{19}F NMR chemical shift of the less shielded pseudo-equatorial fluorine.[18] Clearly, this conformation does not allow any influence of fluorine on the amino group. The distance between an amino proton and fluorine in *trans*-**12b** is approximately 4.2 Å, which is much longer than attractive C–F···H–N contacts (2.4–2.5 Å).[15a] This type of interaction might be expected in conformation **A** (for which both F and NH_3^+, being in pseudo-axial position are closer to each other), but conformer **A** is expected to be unfavourable.

Moreover, some intermolecular contacts were identified in the crystal packing of *trans*-**12b** (Figure 2, d) forming linear chains along the A-axis: intermolecular H-bond between NH- and carbonyl groups (N1–H1···O1, 2.34 Å), C=O···H–C contact (C4–H4···O1, 2.56 Å), and two close C–H···F–C contacts (C3–H3···F1, 2.38 Å; C16–H16···F1, 2.43 Å). Additionally chlorine–chlorine contacts (Cl···Cl, 3.48 Å) were found between two of these linear chains. In contrast, *cis*-**12b** (Figure 2, c) forms dimeric units through intermolecular H-bond contacts between NH- and CO-groups (N1–H01···O1, 2.05 Å). One further weak C=O···H–C contact (C16–H16···O1, 2.69 Å, see Figure 2, c) was observed in the corresponding dimeric unit.

Such a dramatic difference of packing is expected to be the result of a preferable *cisoid*-conformation of the amide bond in *cis*-**12b** (torsion angle O1–C5–N1–H ca. 0°), which leads to favourable formation of dimeric units; in the case of *trans*-**12b**, the corresponding amide bond has *transoid*-conformation (torsion angle O1–C5–N1–H ca. 178°), which leads to the formation of linear chains.

Another approach that has been used to study the influence of fluorine on the basicity of the NH_2 group is to compare pK_a values of fluorinated amines *cis*-**13c** and *trans*-**13a**–**c** and the corresponding non-fluorinated analogues *cis*-**17c** and *trans*-**17a**–**c** (Table 1). The ΔpK_a is approximately 0.8, which is similar to the average pK_a shifts induced by fluorine in γ-fluoroalkylamines.[10d] Moreover, *cis*/*trans*-**13a**–**c** are homologous to 2-fluoro-2-phenyl-cyclopropylamines *cis*/*trans*-**18a**–**c** (Figure 4). Generally, cyclobutane derivatives **13a**–**c** are more basic than **18a**–**c** because the presence of one more CH_2 group between the fluorine and amino groups significantly reduces the through-bond influence of fluorine as electron-withdrawing group. In contrast to cyclobutanes **13a**–**c**, the fluorine effect is more pronounced for cyclopropyl compounds **18**; thus, *trans* isomers, for which F and NH_3^+ are in *syn*-orientation to each other, are more basic then the corresponding *cis* isomers, for which F and NH_3^+ are in *anti*-orientation. This can be ascribed to a hyperconjugative interaction leading to weaker proton affinity of compounds with *anti*- over *syn*-orientation of fluorine and amino functions.[15a,16a] As another result, for *trans*-**13a**–**c**/**18a**–**c** pairs, the ΔpK_a is lower (1.49–1.56) than those of the *cis*-**13b**,**c**/**18b**,**c** pairs (1.85–1.90). On the other hand, the influence of fluorine on the basicity of *cis*/*trans*-**18a**–**c** pairs (ΔpK_a = 0.37–0.40) is more pronounced than in the case of *cis*/*trans*-**13a**–**c** (ΔpK_a = 0.01–0.15).

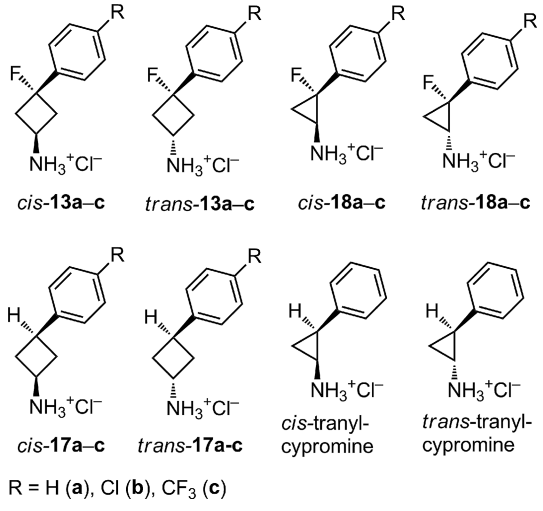


Figure 4. Fluorinated and non-fluorinated phenylcycloalkylamines.

The log *D* values (pH 7.4) were also measured and the log *P* values were calculated by using the pK_a data.[19] In general, *trans*-compounds *trans*-**13a**–**c** are more lipophilic than *cis*-**13a**–**c**, whereas the reverse influence was observed for compounds **6** (see Table 1, entries 1 and 2). Interestingly,

the $\Delta\log P$ between the fluorinated amine *cis*-**13c** and its analogue *cis*-**17c** is only 0.2 units, whereas *trans*-**13b**,**c** are much more lipophilic than their non-fluorinated analogues *trans*-**17b**,**c** ($\Delta\log P \approx 1$). This difference can also be explained by considering favourable conformations for compounds *cis*/*trans*-**13**. Thus, the more favourable conformer **A** of *cis*-**13** is expected to be more polar than conformer **B** of *trans*-**13c** due to their differing dipole moments (Figure 3).

Finally the inhibitor activity against monoamino oxidases A and B (MAO A and MAO B) of synthesised compounds **13**, which are fluorinated homologues of tranylcypromine, was tested. Compounds *cis*-**13a** and *trans*-**13a** were inactive at a maximum test concentration of 200 μM, whereas *trans*-2-phenyl-2-fluorocyclopropylamine (*trans*-**18a**) had IC_{50} values of 12.0 ± 1.0 μM for MAO A and 6.4 ± 0.1 μM for MAO B.[20] This demonstrated the importance of the cyclopropyl core for MAO inhibitors of this type and also supports the anticipated mechanism of action; that is, opening of the cyclopropane ring after oxidation of the amino function.[20,21]

Conclusions

A series of 3-alkyl- (and aryl-) 3-fluorocyclobutylamines has been synthesised and the physicochemical properties of these potential building blocks for drug discovery have been studied. No significant differences in the pK_a values of *cis*/*trans* pairs were found, indicating that through-space interactions between fluorine and the amino function are not present. As expected, fluorinated cyclobutylamines are more acidic than their non-fluorinated counterparts ($\Delta pK_a \approx 0.8$). However, the effect is much smaller than in the case of the corresponding three-membered analogues. Fluorinated *trans*-cyclobutylamines are more lipophilic ($\Delta\log P \approx 1$) than their non-fluorinated analogues, whereas the difference was marginal for *cis* isomers.

Experimental Section

General: Solvents were purified according to standard procedures. Starting materials were purchased from Acros, Merck, Fluka, and Enamine. Melting points are uncorrected. NMR spectra were recorded with a Bruker Avance DRX at 500 MHz (^{1}H), 126 MHz (^{13}C) and 470 MHz (^{19}F) at 25 °C. TMS (for ^{1}H and ^{13}C NMR) and CCl_3F (for ^{19}F NMR) were used as internal standards. Mass spectra (ESI-MS) were measured with a MicroTof Bruker Daltonics instrument. The progress of reactions was monitored by using TLC (silica gel 60 F_{254}, Merck). Column chromatography was carried out on silica gel 60 (Merck, particle size 0.040–0.063 mm). Elemental analyses are correct within the limits of ±0.3% for C, H, N. All starting materials were of the highest commercial quality and were used without further purification. Melting points are uncorrected. Synthetic procedures and characterization data of compounds are given in the Supporting Information.

X-ray Diffraction: Data sets for *cis*-**12b** were collected with a D8 Venture Dual Source 100 CMOS diffractometer. Programs used: data collection: APEX2 V2014.5–0 (Bruker AXS Inc., 2014); cell refinement: SAINT V8.34A (Bruker AXS Inc., 2013); data reduction: SAINT V8.34A (Bruker AXS Inc., 2013); absorption correction, SADABS V2014/2 (Bruker AXS Inc., 2014); structure solution SHELXT-2014 (Sheldrick, 2014); structure refinement SHELXL-2014 (Sheldrick, 2014) and graphics, XP (Bruker AXS Inc., 2014). For *trans*-**12b**, the data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection, COLLECT (R.W.W. Hooft, Bruker AXS, 2008, Delft, The Netherlands); data reduction Denzo-SMN;[22] absorption correction, Denzo;[23] structure solution SHELXS-97;[24] structure refinement SHELXL-97.[25] *R*-values are given for observed reflections, and wR^2 values are given for all reflections.

X-ray Crystal Structure Analysis of *cis*-12b: Formula $C_{15}H_{19}ClFNO_2$; $M = 299.76$; colourless crystal; $0.18 \times 0.18 \times 0.06$ mm; $a = 13.1527(3)$, $b = 10.1230(2)$, $c = 11.9778(2)$ Å, $\beta = 106.216(1)°$; $V = 1531.3(1)$ Å^3; $\rho_{calc} = 1.300$ g cm^{-3}; $\mu = 0.261$ mm^{-1}; empirical absorption correction ($0.954 \leq T \leq 0.984$); $Z = 4$; monoclinic; space group $P2_1/c$ (No. 14); $\lambda = 0.71073$ Å; $T = 223(2)$ K; ω and φ scans, 9458 reflections collected ($\pm h$, $\pm k$, $\pm l$), 3080 independent ($R_{int} = 0.033$) and 2716 observed reflections [$I > 2\sigma(I)$], 188 refined parameters, $R = 0.047$, $wR^2 = 0.114$, max. (min.) residual electron density 0.25 (–0.32) e Å^{-3}. The hydrogen at N1 atom was refined freely; others were calculated and refined as riding atoms.

X-ray Crystal Structure Analysis of *trans*-12b: Formula $C_{15}H_{19}ClFNO_2$; $M = 299.76$; colourless crystal; $0.18 \times 0.12 \times 0.11$ mm; $a = 5.3865(2)$, $b = 10.5060(4)$, $c = 13.8052(5)$ Å, $\alpha = 109.241(2)°$, $\beta = 93.483(2)°$, $\gamma = 91.201(2)°$; $V = 735.5(1)$ Å^3; $\rho_{calc} = 1.353$ g cm^{-3}; $\mu = 2.415$ mm^{-1}; empirical absorption correction ($0.665 \leq T \leq 0.772$); $Z = 2$; triclinic; space group $P\bar{1}$ (No. 2); $\lambda = 1.54178$ Å; $T = 100(2)$ K; ω and φ scans, 7404 reflections collected ($\pm h$, $\pm k$, $\pm l$), 2682 independent ($R_{int} = 0.034$) and 2318 observed reflections [$I > 2\sigma(I)$], 188 refined parameters, $R = 0.037$, $wR^2 = 0.102$, max. (min.) residual electron density 0.29 (–0.20) e Å^{-3}. The hydrogen at N1 atom was refined freely, but with N–H distance restraints (SADI, DFIX); others were calculated and refined as riding atoms.

pK_a Measurements: The pK_a values of *cis*/*trans*-**6**, **13a**–**c**, **17a**,**b** were measured with a titrator SI Analytics TitroLine® 7000 with the dosing unit WA 20 mL. The values were calculated by using the software TitriSoft 3.0. A quantity of 5–10 mg of the corresponding amine hydrochlorides was dissolved in 500 μL of 2 M hydrochloric acid and 10 mL of 0.1 M potassium nitrate solution. The resulting test solution was titrated against 0.1 M sodium hydroxide solution.

log *D* Measurements: The $\log D$ values of *cis*/*trans*-**6**, **13a**–**c**, **17a**,**b** were measured by using a miniaturised shake-flask method. Compounds were dissolved in the previously mutually saturated mixture containing 990 μL of phosphate-buffered saline (PBS, pH 7.4) and 100 μL of *n*-octanol, followed by mixing on a rotator for 1 h at 30 rpm. Equilibrium distribution of each compound between the organic phases was determined by using LC-MS (Shimadzu VP HPLC system, API3000 mass-detector, AB Sciex). Analytic concentrations were measured in both phases, in duplicate.

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